Solution-Phase Parallel Synthesis of Hsp90 Inhibitors

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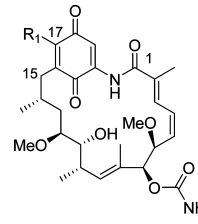
As part of an oncology chemistry program directed toward discovery of orally bioavailable inhibitors of the 90 kDa heat shock protein (Hsp90), several solution-phase libraries were designed and prepared. A 2 × 89 library of racemic resorcinol amides was prepared affording 131 purified compounds. After evaluation in a binding assay, followed by an AKT-Luminex cellular assay, three potent analogs had functional activity between 0.1 and 0.3 μM. Resolution by preparative chiral SFC chromatography led to (+)-**15**, (+)-**16**, and (+)-**17** having functional IC_{50} = 27, 43, and 190 nM, respectively. (+)-**15** exhibited high clearance in human hepatocytes driven primarily by glucuronidation as confirmed by metabolite identification. A second 8 × 14 exploratory library was designed to investigate heterocyclic replacements of the resorcinol ring. The second library highlights the use of the (−)-sparteine-mediated enantioselective Pd-catalyzed α-arylation of *N*-Boc-pyrrolidine to prepare chiral 2-arylpyrrolidines in parallel.

Introduction

Heat shock protein 90 (Hsp90) is an ATP-dependent molecular chaperone responsible for the stability and maintenance of client proteins.[1] It has emerged as an attractive target for cancer therapy in large part because its client proteins are overexpressed in cancer and are responsible for cancer proliferation and survival. Inhibition of Hsp90 causes destabilization and degradation of oncogenic client proteins providing a means to limit or stop cancer cell growth.[2] For example, inhibition of Hsp90 has been shown to induce apoptosis in cancer cells through inhibition of the PI3K/Akt pathway.[3] Other client proteins important for cell growth and survival include Her2, cKit, MET, Hif-1α, and the androgen receptor making Hsp90 a major target in oncology research as it creates an opportunity to disrupt multiple oncogenic proteins simultaneously.

Discovery of small molecule inhibitors of Hsp90 remains an active field of research and has been extensively reviewed.[4] Hsp90 is an ATPase with an ATP-binding cleft within the N-terminal domain of the protein. Most antitumor compounds under current investigation bind in this cleft including the natural product geldanamycin (**1**)[5] and its analogs 17-AAG (**2**)[6] and 17-DMAG (**3**)[7] (Figure 1). These and other ansamycin analogs, including hydroquinone derivatives of 17-AAG,[8] have been studied in clinical and preclinical settings but suffer from poor solubility and hepatototoxicity believed to be, in part, caused by the benzoquinone toxicophore common in **1**−**3**.[9] A number of research groups have reported the discovery and cocrystal structures of phenol and bis-phenol containing inhibitors of Hsp90. These include the natural product radicicol,[10] diarylheterocycles containing 2,4-hydroxyphenyl-isoxazoles, and 2,4-hydroxyphenyl-pyrazoles,[11] chimeric molecules containing the resorcinol from radicicol,[12] and a patent application from Chessari and co-workers.[13] Kung and co-workers have disclosed the identification of resorcinol bis-amides derived from the screening hit **PD-180854**.[14] A common drawback of phenol containing Hsp90 inhibitors is the large clearance risk due to the high probability for clearance via a glucuronidation pathway. Glucuronidation as the pathway for clearance of the compounds described in this report was initially indicated by examining metabolic stability in human hepatocytes and human liver microsomes. In most cases, compounds such as **24** (Table 2) show high clearance in human hepatocytes (intrinsic Cl = 26 μL/min/million cells) and low to moderate clearance in human liver microsomes (intrinsic Cl = 8.9 mL/min/kg), indicating a phase II clearance mechanism. This mechanism was later established using mass spectroscopy to identify a monoglucuronide adduct after incubation of **24** in human liver microsome cocktail containing UDPGA and NADPH. A single major *O*-glucuronide was observed with very little of a second regioisomer and none of the bis-*O*-glucuronide. Consequently, the site of glucuronidation was presumed to be at



geldanamycin, **1** R_1=OMe
17-AAG, **2** R_1=$NHCH_2CH{=}CH_2$, Ki = 388 nM, IC_{50} = 29 nM
17-DMAG, **3** R_1=$NHCH_2CH_2N(CH_3)_2$, Ki = 469 nM, IC_{50} = 30 nM

Figure 1. Ansamycins: geldanamycin (**1**) and synthetic analogs 17-AAG (**2**) and 17-DMAG (**3**).

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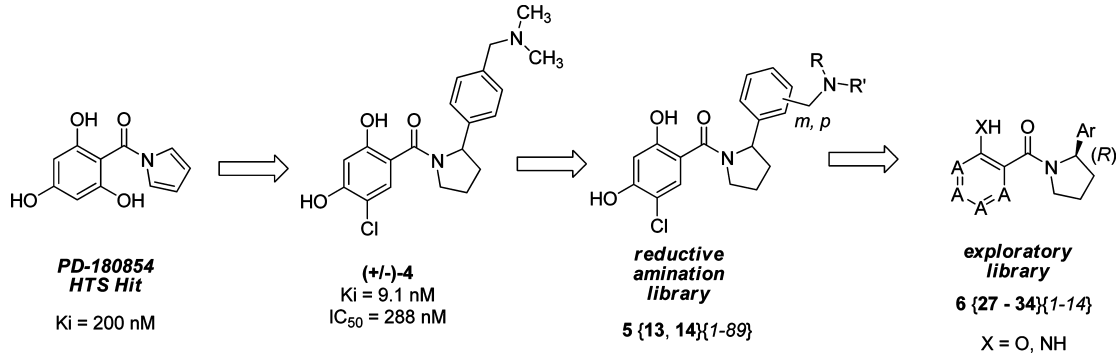
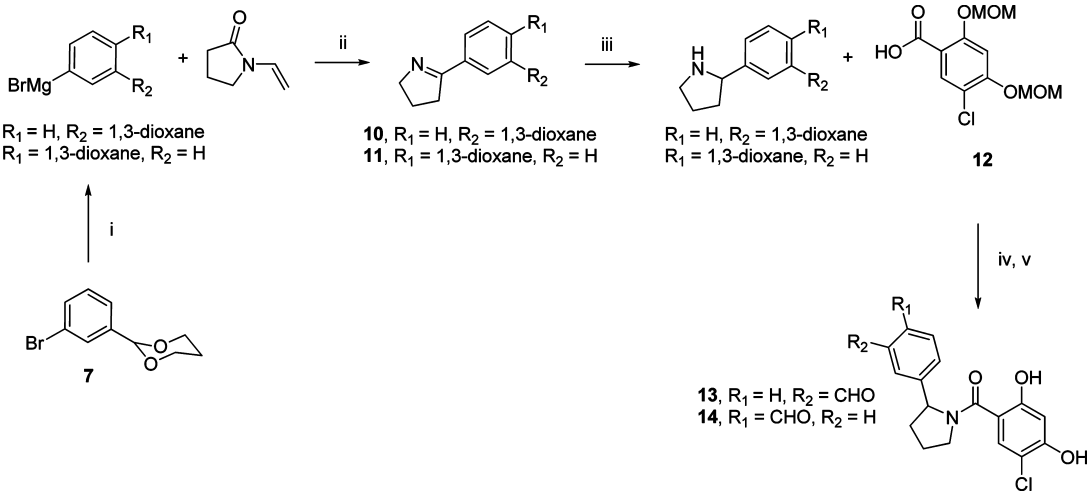


Figure 2. General description of libraries.

Scheme 1. Synthesis of Aldehydes **13** and **14**[a]



[a] Reaction conditions: (i) Reike Mg (1.2 equiv), THF; (ii) THF, 0−25 °C, 30 min; (iii) $NaBH_4$ (2 equiv), iPA; (iv) EDCI (1.1 equiv), HOBt (1.1 equiv), NMM (1.1 equiv), DMA, 25 °C, 2 h; (v) TFA, DCM for **13**; 0.5 M HCl, MeOH, for **14**.

one of the two phenolic oxygens of the resorcinol ring. In our first library, we sought to reduce glucuronidation through the strategy of lowering lipophilicity by incorporation of a basic amine. This strategy is supported by QSAR studies on different UGT substrates and different UGT isoforms, indicating that hydrophobicity is a major feature of being a good UGT substrate. This QSAR observation is reinforced by a membrane topology model, in which localization of the substrate in the cell membrane first, may lead to enhanced access to the UGT active site.[15] The strategy to improve clearance by lowering lipophilicity led to reductive amination library **5** (Figure 2), where the basic amine was placed off the para- and meta-positions of a 2-arylpyrrolidine ring. A second and related amide bond library (**6**) is also described herein. This second library had the goal of examining potential replacements of the resorcinol ring with heterocyclic acids. In this design, 14 heterocyclic acids were selected, which displayed an OH, SH, or NH_2 group in the 2- or 4-position relative to the acid in an attempt to mimic the hydrogen bonding interactions of the recorcinol ring with Hsp90. The amine component of library **6** was designed to maintain optimal chirality (R configuration) and para-substitution off the 2-arylpyrrolidine, a motif discovered from library **5**. The preparation of chiral 2-arylpyrrolidines for library **6** highlights Kevin Campos' enantioselective Pd-catalyzed α-arylation of N-Boc-pyrrolidine to prepare enantioenriched 2-arylpyrrolidines in parallel. This is a powerful method to efficiently synthesize diverse 2-arylpyrrolidines having the desired chirality for this class of Hsp90 inhibitors. A general description of the hit to lead progression and libraries **5** and **6** is outlined in Figure 2.

Results and Discussion

(±)-**4** (Figure 2) represents the lead compound for the reductive amination library. The binding potency of 9.1 nM indicated that a benzylic amine is tolerated off the para position of the aromatic ring of the 2-phenylpyrrolidine. However, the moderate cellular potency of 288 nM was one attribute in need of improvement. In addition, the risk of high clearance because of phenol glucuronidation was a general concern based on metabolite identification studies of closely related compounds discovered prior to those described in this report. Our strategy was to utilize a library approach to examine the feasibility of finding a small cohort of compounds having overlap of metabolic stability in human hepatocytes and improved cellular potency.

Synthesis of the Scaffolds. Synthesis of aldehyde templates **13** and **14** on a 3 g scale is depicted in Scheme 1. Grignard reagent **8** was prepared in one step from commercially available 1-bromo-3-(1,3-dioxane-2-yl)benzene (**7**), while **9** was purchased from Reike Metals. The addition of each Grignard reagent to *N*-vinyl pyrrolidinone resulted in formation of the 2-pyrrolines, **10** and **11**, in 23% and 29% yield after purification by silica gel chromatography. It was

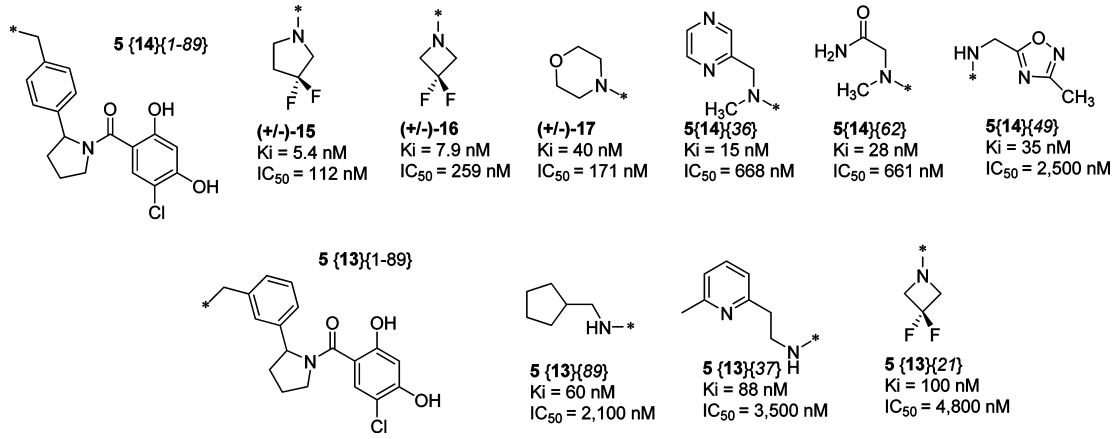


Figure 3. Biological activity of selected library members.

interesting to note that these cyclic imines were stable to silica gel chromatography and showed no evidence of hydrolysis or decomposition on thin layer chromatography plates. Reduction of the 2-pyrrolines using $NaBH_4$ was followed by amide bond formation with acid **12**.[14] Finally, deprotection of the MOM and acetal groups was accomplished using TFA in DCM for **13** and methanolic HCl for **14**. The different deprotection conditions were based on the chemists' preference, not because of solubility or other reasons. Both deprotection methods (TFA in DCM and HCl in MeOH) afforded similar yields (71% for **13**, 78% for **14**).

Synthesis of Library 5. Preferred reaction conditions for reductive amination involve using DCM as the solvent and $NaBH(OAc)_3$ as the reducing agent because of the ease of removal of the DCM following the reaction and the good yield and purity this method generally provides. While aldehyde **13** was soluble in DCM, **14** was not. As a consequence, DMSO was selected as the reaction solvent for template **14**. Therefore, library **5** was split into two production runs based on these solubility differences, with each production run having slightly different reaction conditions. Hence, for **5**{**13**}{*1*−*89*}, one equivalent of **13** was reacted with 1.05 equivalents of amine **5**{*1*−*89*} (see the Supporting Information for the amine structures) in DCM using $NaBH(OAc)_3$ (1.5 equiv) in the presence of HOAc (0.1 equiv). After 18 h at ambient temperature, the reaction mixtures were quenched with MeOH and the solvents were removed. The products were then dissolved in DMSO and purified via reverse phase HPLC. After purification, 64 compounds passed QC (>80% purity in both TIC and UV, 254 nM). For **5**{**14**}{*1*−*89*}, DMSO was used as the reaction solvent and 2.5 equivalents of $NaBH(OAc)_3$ were used. After 1 h at ambient temperature, the reaction mixtures were quenched with MeOH and the products were purified via reverse phase HPLC (see Supporting Information for HPLC conditions). After purification, 67 compounds passed QC (>80% purity in both TIC and UV, 254 nM). The 131 purified compounds were then assayed for biological activity.

Evaluation of Biological Activity. Hsp90 activity was determined using a tritium labeled displacement assay, followed by a triage process to select the most potent binders for further evaluation in a functional assay. The reported K_i was determined using a competitive binding assay, in which the ability of test compounds to displace a tritium-labeled ligand from Hsp90 was measured. The functional assay then measured the degradation of Hsp90 client protein Akt in H1299 lung cancer cells and is reported as an IC_{50} (see Supporting Information for a description of the assay). Figure 3 shows biological data for nine representative compounds potent enough in the competitive binding assay to progress into the functional assay. The most active compounds came from reductive amination of *para*-aldehyde **14**, resulting in six compounds with $IC_{50} < 1$ uM. The most potent compound was resynthesized and characterized as (±)-**15**. To gain a better understanding of the ligand-protein interactions, a 1.95 Å cocrystal structure of (±)-**15** was obtained (RCSB ID code rcsb053037 and PDB ID code 3HEK).

The cocrystal structure shows (*R*)-**15** bound in the ATP binding cleft near the N-terminal domain of the protein (Figure 4, left). The key ligand−protein interactions of the resorcinol ring with Hsp90 are described elsewhere but without a discussion of the impact of stereochemistry. Since the stereochemistry at the 2-position of the pyrrolidine ring plays a key role to binding and is a focal point of this work, it is discussed here in more detail. The 3,3-difluoropyrrolidine reaches into a hydrophobic region bounded by Tyr137, Val136 and Gly135 thereby picking up favorable interactions. A model of (*S*)-**15** was built into the same binding pocket using Pfizer's MoViT software v3.0 (see Supporting Information for a description of the algorithm). The resorcinol ring was restrained to maintain the hydrogen bonding network known to be important for potency (see ref 18). Protein−ligand minimization while constraining the resorcinol ring resulted in a model of (*S*)-**15** (Figure 4, right). The docking protocol placed the 2-phenyl substituent of the pyrroldine ring in the same general region occupied by the 2-phenyl substituent of the (R)-isomer. This is likely to afford similar favorable hydrophobic interactions but to accommodate this, rotation around the N−C(O) bond of the tertiary amide is required. This ninety-degree amide conformation creates a large amount of ligand strain since the tertiary amide can no longer adopt a coplanar arrangement of the pyrrolidine ring nitrogen with the amide carbonyl. On the basis of the observations that (*R*)-**15** preferentially cocrystallized from a racemic mixture of (±)-**15** *and* that a simple docking model indicates a high degree of ligand strain for (*S*)-**15**, it was

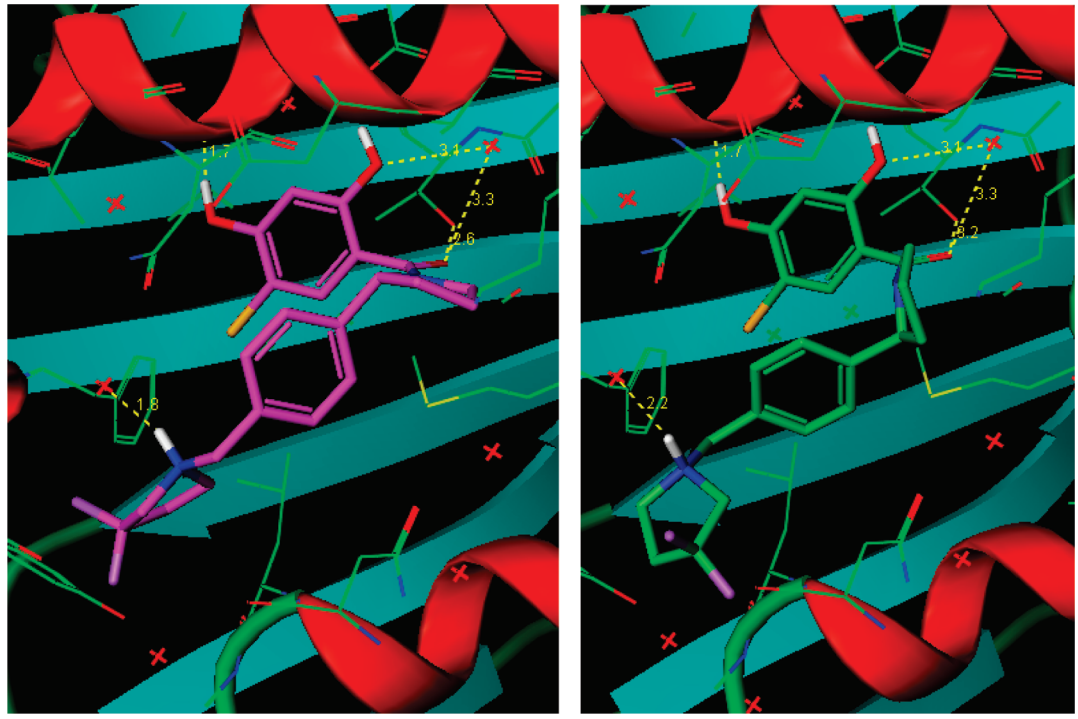


Figure 4. (left, purple) 1.95 Å cocrystal structure of (*R*)-**15** in the N-terminal ATP binding domain of human cytosolic HSP90α, residues 9−225 with C-terminal His-tag, and (right, green) a strained model of (*S*)-**15**.

concluded that the (R)-isomer represents a better fit and would bind to Hsp90 in a much lower energy conformation compared to the (S)-isomer. Our attention then turned toward resolution of the three most potent library members to characterize the activity of the single enantiomers.

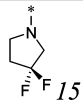
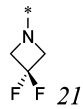
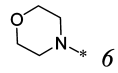
Biological Activity of Single Enantiomers. Racemic library members derived from reductive amination using amines *6*, *15*, and *21* with aldehyde **14** were resynthesized and characterized as (±)-**15**, (±)-**16**, and (±)-**17** (Figure 3). The racemic mixture was resolved using chiral supercritical fluid chromatography (SFC). Each enantiomer was then re-evaluated in the biological assays and the results are shown in Table 1. Single enantiomers (+)-**15**, (+)-**16**, and (+)-**17** had binding activity of 3.5, 2.0, and 24 nM, respectively, with functional activity of 27, 43, and 190 nM. Unfortunately, all three compounds exhibited high clearance in human hepatocytes with (+)-**15** having a half-life of 22 min. On the basis of metabolite identification studies ongoing at the time, it was hypothesized that the major clearance mechanism for (+)-**15** was glucuronidation at either the 2-OH or 4-OH of the resorcinol ring.[16]

Synthesis of Chiral-2-Arylpyrrolidines. Since our earlier work had established that the (R)-enantiomer 2-arylpyrrolidine resorcinol amides are significantly more potent than the (S)-enantiomers, we began to investigate enantioselective methods to create the R stereocenter, while at the same time thinking about strategies to address clearance. A method from the literature that suited our synthetic need was the (−)-sparteine-mediated enantioselective Pd-catalyzed α-arylation of *N*-Boc-pyrrolidine originally pioneered by Peter Beak and further developed by Kevin Campos and co-workers at Merck.[17] Notably, (+)-sparteine is not commercially available, so it was fortunate that our requirement for the R-isomer matched the stereochemistry delivered by the natural form of (−)-sparteine.[18] The synthesis of the chiral 2-arylpyrrolidines from aryl and heteroaryl bromides is straightforward and enabled further investigation of the SAR off the 2-position of the pyrrolidine ring while installing the correct stereochemistry at the same time (Scheme 2).

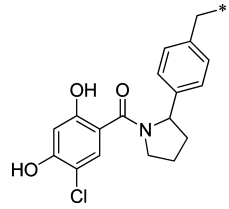
For parallel medicinal chemistry, an excellent feature of the chemistry is the stereochemical stability of organozinc **18**. Although the stereochemical stability of 2-lithio-*N*-Boc-pyrrolidine is compromised at temperatures above −60 °C,[19] transmetalation with $ZnCl_2$ affords organozinc **18**, which can be warmed to room temperature and subdivided into separate aliquots without any loss of stereochemical integrity. Singleton resorcinol amides were prepared from enantioenriched 2-arylpyrrolidines and screened in the Hsp90 assays (Table 2). Compounds **19**−**26** displayed nanomolar activity in the binding assay while the cellular potency varied between 0.21 and 5.2 μM. High clearance remained an issue for **19**−**26** prompting the desire to move away from the resorcinol ring system.

Examining potential replacements of the resorcinol ring was the primary goal of the second amide bond library (**6**). The acid components were selected from readily available heterocycles, which display an OH, SH, or NH_2 group in either the 2- or 4-position relative to the acid. It was anticipated that these H-bond donors would mimic at least one of the resorcinol hydroxyls, thereby maintaining either the key hydrogen bond from the 2-OH group of the resorcinol to the side chain COOH of Asp-93 or the other key hydrogen bond from the 4-OH to a conserved water bound to Ser52 of Hsp90. The goal of the library was to find a new lead with 1−5 μM binding affinity for Hsp90.[20] While exploring the potential for hydrogen bonding interactions from the

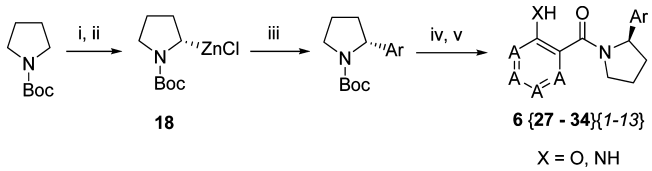
Table 1. Data for Single Enantiomers

Compound	*Amine*	*absolute configuration*[a]	*Ki (nM)*[b]	*IC_{50} (nM)*[b]	*specific rotation $[\alpha]_D$*	*% ee by chiral SFC*
(+)-15	 *15*	(+)-R	3.5	27	+ 135	100
(-)-15	*15*	(-)-S	2,500	> 10,000	- 139	100
(+)-16	 *21*	(+)-R	2.0	43	+ 136	100
(-)-16	*21*	(-)-S	3,600	> 10,000	- 136	100
(+)-17	 *6*	(+)-R	24	190	+ 145	100
(-)-17	*6*	(-)-S	21,000	> 10,000	- 149	100

[a] The absolute configuration is inferred from cocrystal structures of similar compounds prepared using the (−)-sparteine-mediated enantioselective Pd-catalyzed α-arylation of N-Boc-pyrrolidine. [b] The assay error for both assays is 10−15%, and the numbers reported are the average of two assay duplicates ($n = 2$).



Scheme 2. Synthesis 2-Arylpyrrolidines and Library **6**[a]



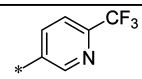
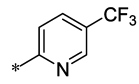
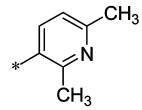
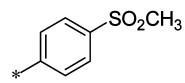
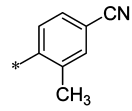
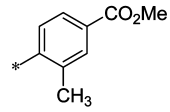
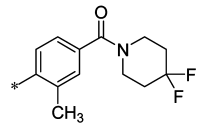
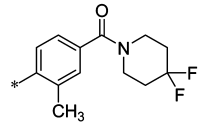
[a] Reaction conditions: (i) *s*-BuLi (1 equiv), (−)sparteine (1 equiv), −78 °C, MTBE/cyclohexane, 5 h; (ii) $ZnCl_2$ (1 equiv), THF, −78−20 °C, 18 h; (iii) ArBr (1 equiv), $Pd(OAc)_2$ (0.05 equiv), tBu_3P-HBF_4 (0.06 equiv), THF, 24 h; (iv) HCl, 1,4-dioxane, DCM, 3 h; (v) acid (1.1 equiv), HATU (1.1 equiv), Et_3N (3 equiv), DMF, 20 °C, 18 h.

heterocyclic acids, the amine components of the library were designed to maintain optimal chirality (*R* configuration) of the 2-arylpyrrolidine and para-substitution off the aryl ring. This amine motif had optimal characteristics nicely filling a large pocket in Hsp90 formed by the side chains of residues Tyr137, Val136, and Gly135. Amines **27** and **30** were incorporated into the library as controls since it was already known that the products of amide bond formation of (±)-**27** and **30** with 5-chloro-2,4-dihydroxybenzoic acid gave rise to products having binding potency of 27 and 54 nM, respectively (**24** and **19**, Table 2). The Campos method enabled efficient preparation of **27**−**34** in parallel on 1−1.5 g scale from a single batch of the chiral zinc reagent, **18**, without the use of a glovebox. The isolated yields for **27**−**34** from the corresponding aryl bromide are shown in Figure 5. In all cases, the measured enantiomeric ratio of the products was 96:4 or better as determined by chiral SFC chromatography. Synthesis of library **6**, began with Boc removal from **27**−**34** using HCl in 1,4-dioxane/DCM at room temperature. After removal of the solvents, the pyrrolidine HCl salts were dissolved in DMF. Et_3N (3 equiv) was added, followed by the heterocyclic acids **6**{*1*−*14*}, and the amide bond formation was accomplished using HATU as the coupling reagent. Purification via reverse phase HPLC afforded 76 compounds passing QC (>80% purity in both TIC and UV, 254 nM), representing a 68% success rate. Good representation from the heterocyclic acids was noted as shown in Figure 5 (green = successful, red = unsuccessful) with 2-amino-5-bromonicotinic acid **6**{*14*} as the exception which failed to afford any amide product from all 8 reactions attempted. Hsp90 binding affinity was examined by measuring percent inhibition at 1 and 10 μM. Unfortunately, none of the 76 compounds demonstrated activity when tested at 10 μM in the binding assay. This lack of binding is presumably the result of the shortcomings of the heterocyclic acids to create the same binding interactions as the 5-chloro-2,4-dihydroxybenzamides described earlier.

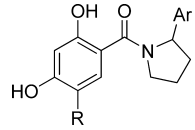
Summary and Conclusions

A 2 × 89 reductive amination library (**5**) afforded three potent racemic Hsp90 inhibitors (±)-**15**, (±)-**16**, and (±)-

Table 2. Singleton Hsp90 Inhibitors

Compound	*Ar*	*R*	*Ki (nM)*	*IC_{50} (nM)*	*stereochemistry*[a]
19		Cl	54	5200	*R* (er 96 : 4)
20		Cl	34	5200	*R* (er 96 : 4)
21		Cl	38	4900	*R* (er 96 : 4)
22		Cl	19	1000	*R* (er 96 : 4)
23		Cl	14	400	*R* (er 96 : 4)
24		Cl	27	1000	*racemic*
25		Cl	3.9	210	*R* (er 96 : 4)
26		CH_3	14	450	*R* (er 96 : 4)

[a] The stereochemical assignment is based on the established outcome of the (−)-sparteine-mediated enantioselective Pd-catalyzed α-arylation of *N*-Boc-pyrrolidine. Enantiomeric ratio (er) was measured using chiral SFC (area %).



17. Resynthesis and resolution via preparative chiral SFC led to (+)-**15** with 27 nM potency for AKT degredation in H1299 cells. The level of potency for (+)-**15** is equivalent to DMAG and is ten times more potent than the lead compound (±)-**4**. Cocrystallization studies with (±)-**15** led to the conclusion that the *R* enantiomer of the pyrrolidine ring is optimal for maintaining planarity of the amide carbonyl with the pyrrolidine ring while extending the aryl group into a hydrophobic pocket of Hsp90. This discovery led to the use of an enantioselective method from the literature to create enriched compounds (er 96:4) with the preferred chirality. Ultimately, the strategy of lowering lipophilicity by incorporation of basic amines proved unsuccessful in part because our most potent compounds had an electron-withdrawing group (*gem*-difluoro or oxygen) on the pyrrolidine or azetidine ring reducing the basicity of the amine and therby increasing the logD. A different strategy was then examined, which involved replacing the offending hydroxyls with heterocyclic acids that display an OH, SH, or NH_2 group in either the 2- or 4-position relative to the acid. This approach led to exploratory library **6**, in which the amine components were synthesized using the (−)-sparteine-mediated enantioselective Pd-catalyzed α-arylation of *N*-Boc-pyrrolidine to provide gram quantities of chiral (2*R*)-aryl-*N*-Boc-pyrrolidines in parallel. Although this library did not meet its goal of finding compounds with 1−5 μM Hsp90 binding potency, the pool of starting materials came from a limited selection of commercially available heterocyclic acids. Structure-based design of custom hydrogen bonding fragments is a logical next step to consider and

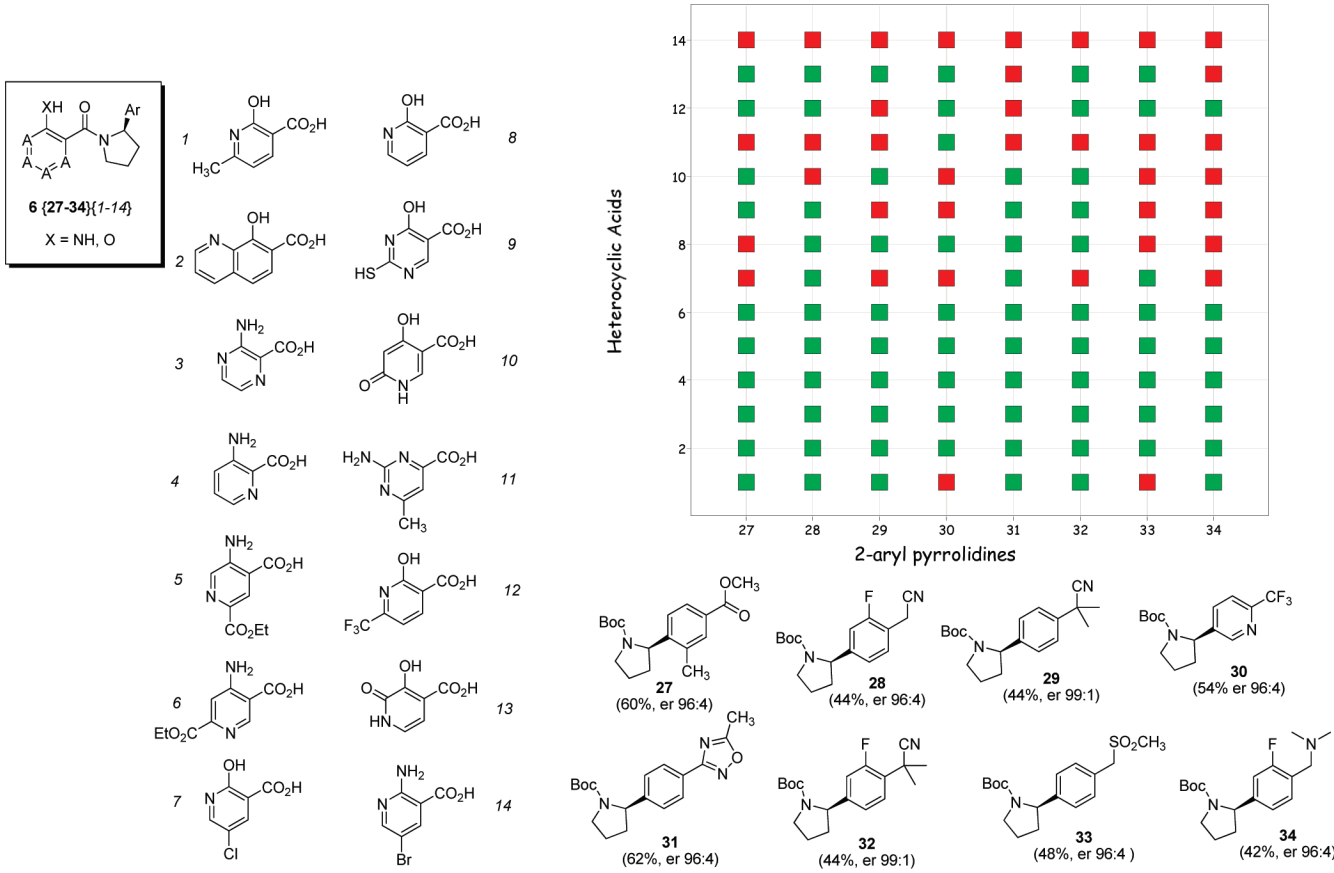


Figure 5. Library **6** to investigate resorcinol replacements for Hsp90 (green = purified and tested, red = unsuccessful well).

would benefit from phenol bioisostere considerations[21] and hybrid designs using SAR from other chemical series under investigation.

Experimental Section

General Methods. Anhydrous solvents were purchased from Aldrich in Sure-Seal bottles and chemicals from commercial sources were used without further purification. Reactions were routinely run under a dry nitrogen blanket using standard techniques. Synthesis of the library was performed in a 96-well format in 10 × 75 mm glass test tubes sealed with parafilm. Reactions were monitored by LCMS and thin layer chromatography using either UV light or *p*-anisaldehyde stain to visualize. Depending on the scale, evaporation of the solvents was performed on a rotary vacuum evaporator (Buchi) or SpeedVac concentrator (Thermo Savant, now part of ThermoFisher) or GeneVac concentrator (GeneVac, Ltd.).

^{1}H NMR spectra of the synthetic intermediates, and final products were obtained using a Burker instrument operating at 400 MHz and ^{13}C NMR spectra were recorded at 75 MHz. NMR spectra were obtained in the solvents stated using residual protonated solvent as an internal standard. When using $CDCl_3$, the reference was set with the $CHCl_3$ peak at 7.26 ppm. When using DMSO-d_6, the reference was set at 2.50 ppm. Analysis and purification of library compounds to afford 30 mM DMSO stock solutions was accomplished as described in Ventura et al.[22] The synthesis of compound **24** has been described previously.[14] Aryl bromide starting materials for the synthesis of **27**, **30**, **31**, and **33** are commercially available. Aryl bromide starting materials for **28** and **32** were prepared as described in ref 23. The preparation of the starting material for **29** is described in ref 24. For **32**, dimethyl amine alkylation using the conditions of ref 25 were applied using 4-bromo-1-(bromomethyl)-2-fluorobenzene, which was synthesized as described in ref 23.

5-(3-(1,3-Dioxan-2-yl)phenyl)-3,4-dihydro-2*H*-pyrrole (10). A 500 mL round bottom flask fitted with an addition funnel was charged with Reike Mg (2.5 g Mg, 100 mmol, suspension in 100 mL THF), and the resulting suspension cooled to 0 °C. 2-(3-bromophenyl)-1,3-dioxane (20.8 g, 85.7 mmol) was dissolved in THF (80 mL) and slowly added to the stirred suspension of Reike Mg over a period of 30 min. The ice bath was removed toward the end of the 30 min addition, and the reaction was allowed to stir for an additional 30 min at room temp. The formation of the Grignard reagent was monitored by checking the LCMS of the MeOH quenched reaction solution. The Grignard reagent was cooled to 0 °C, and 1-vinylpyrrolidin-2-one (9.53 g, 85.7 mmol) was added dropwise as a solution in THF (60 mL). After the addition was complete, the ice bath was removed, and the reaction mixture was warmed to room temperature. After 30 min at room temperature, LCMS and TLC analysis showed the reaction to be complete. The reaction mixture was cooled to 0 °C and quenched by the dropwise addition of water (100 mL). The quenched reaction was further diluted with water (150 mL) and Et_2O (300 mL) and transferred to a separatory funnel. Saturated aq. NaCl was added, as well as saturated aq. KH_2PO_4, to help the phases separate and to

bring the pH of the aqueous layer to pH 6. The aqueous layer was extracted with Et_2O (×4), and the combined organic extract was washed with aq. $NaHCO_3$, brine and dried over $MgSO_4$. After removal of the solvents, 17 g of a viscous red oil was obtained. This oil was purified via flash chromatography eluting with a slow gradient of 5−30% EtOAc in hexanes, holding at 30% for 5 CV, then ramping from 30−75% EtOAc in hexanes. After the fractions of interest were collected, 4.5 g (23% yield) of the desired product was obtained as a yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 1.46 (d, J = 13.35 Hz, 1 H) 1.72 (br. s., 1 H) 2.04 (qd, J = 7.81, 7.55 Hz, 2 H) 2.16−2.32 (m, 1 H) 2.97 (t, J = 8.06 Hz, 2 H) 3.95−4.02 (m, 1 H) 4.02−4.10 (m, 2 H) 4.28 (dd, J = 11.33, 5.04 Hz, 2 H) 5.54 (s, 1 H) 7.42 (t, J = 7.68 Hz, 1 H) 7.56 (d, J = 7.30 Hz, 1 H) 7.86 (d, J = 7.81 Hz, 1 H) 7.94 (s, 1 H). APCI-MS: *m/z* 250 ($M^+ + H_2O$) corresponding to either the ring-opened aminoketone or the ring-closed hemiaminal or an equilibrium mixture of the two.

5-(4-(1,3-Dioxan-2-yl)phenyl)-3,4-dihydro-2*H*-pyrrole (11). To a solution of vinyl-2-pyrrolidinone (8.34 g, 75 mmol) in THF (60 mL) cooled to 0 °C was added dropwise the Grignard reagent (**9**) (250 mL, 0.25 M in THF, 62 mol). After the addition was complete, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride (100 mL). The quenched reaction was further diluted with water (150 mL) and Et_2O (300 mL) and transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (×3). The combined organics were washed with aqueous saturated NaCl and then dried over $MgSO_4$. Purification was accomplished by silica gel chromatography using a gradient of 30−50% EtOAc in hexanes. Collection and concentration of the pure fractions afforded 4.03 g (29%) of compound **11** as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.35−1.56 (m, 1 H) 1.82−2.12 (m, 3 H) 2.77−3.00 (m, 2 H) 3.83−4.02 (m, 4 H) 4.06−4.23 (m, 2 H) 5.55 (s, 1 H) 7.45 (d, J = 8.31 Hz, 2 H) 7.81 (d, J = 8.31 Hz, 2 H). APCI-MS: *m/z* 250 ($M^+ + H_2O$) corresponding to either the ring-opened aminoketone or the ring-closed hemiaminal or an equilibrium mixture of the two.

3-(1-(5-Chloro-2,4-dihydroxybenzoyl)pyrrolidin-2-yl)-benzaldehyde (13). 5-(3-(1,3-Dioxan-2-yl)phenyl)-3,4-dihydro-2*H*-pyrrole (**10**) (4.5 g, 19 mmol) was dissolved in *i*PrOH (100 mL), and $NaBH_4$ (1.5 g, 39 mmol) was added in 0.2 g portions until the full 1.5 g was added. The reaction mixture was allowed to stir at room temperature for 16 h, and the excess $NaBH_4$ was quenched by the addition of MeOH (100 mL). After the quenched mixture was stirred for 15 min, the solvents were removed on the rotovap, and MeOH (100 mL) was added again. The mixture was stirred for another 15 min, and the MeOH removed on the rotovap again. A third round of MeOH treatment was conducted, and the crude mixture was dried by placing on high-vac for 16 h. The crude NH-pyrolidine was taken to the next step without further purification. The NH-pyrrolidine (4.43 g, 19 mmol) was dissolved in DMA (25 mL). Acid **12**[13] (5.3 g, 19 mmol) was dissolved in DMA (50 mL) and added to the amine solution. HOBt (2.8 g, 21 mmol), *N*-methylmorpholine (2.3 mL, 21 mmol), and EDCI (4.0 g, 21 mmol) were added sequentially, and the reaction was stirred at room temperature for 5 min. The reaction was then heated to 50 °C for 15 min and allowed to cool back to room temperature. After 2 h, the reaction was checked by LCMS, which indicated that clean, complete amide bond formation had taken place. The reaction mixture was partitioned between water (80 mL) and EtOAc (100 mL). The organics were extracted into EtOAc (3 × 150 mL), and the combined organic extract was washed with saturated aq. $NaHCO_3$ (×3) and brine (×1) and dried over MgSO4. After removal of the solvent, the dark red oil was purified via flash chromatography eluting with a gradient of 10−80% EtOAc in PetEther. The fractions were analyzed by TLC eluting with 60% EtOAc in PetEther, and those containing pure product were combined to afford the desired amide adduct, 7.15 g (76%), as a yellow oil. The amide adduct (6.5 g, 13 mmol) was dissolved in DCM (100 mL), and TFA (60 mL) was added, followed by water (100 mL). The two-phase mixture was stirred vigorously for 4 h, at which time TLC showed complete deprotection of the MOM and acetal protecting groups. After the reaction was complete, the DCM and 50% of the TFA were removed via rotovap. Water (100 mL) was added, and the product was extracted into Et_2O (3 × 100 mL). The combined organic extract was washed with saturated aqueous K_2CO_3 (**Caution!** *foaming*), water, and brine. After the mixture was dried over $MgSO_4$, the solvents were removed to afford a brown oil. This oil was purified via flash chromatography, eluting with a gradient of 12−70% EtOAc in hexanes, and the desired fractions were combined to afford 3.3 g (71%) of **13** as a white foam. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 1.95 (d, J = 3.02 Hz, 2 H), 2.10 (br. s., 1 H), 2.50 (br. s., 1 H), 3.92−4.08 (m, 2 H), 5.32 (t, J = 7.43 Hz, 1 H), 6.56 (s, 1 H), 7.41−7.65 (m, 3 H), 7.73−7.86 (m, 2 H), 10.01 (s, 1 H). APCI-MS: *m/z* 346 ($M^+ + H$).

4-(1-(5-Chloro-2,4-dihydroxybenzoyl)pyrrolidin-2-yl)-benzaldehyde (14). 5-(4-(1,3-Dioxan-2-yl)phenyl)-3,4-dihydro-2*H*-pyrrole (**11**) (44 g, 19 mmol) was dissolved in 20% acetic acid in methanol (100 mL), and $NaBH_4$ was added (76.4 mL of 0.5 M in diglyme, 38 mmol). The reaction was allowed to stir at room temperature for 16 h, and the excess $NaBH_4$ was quenched by the addition of MeOH (100 mL). After the quenched mixture was stirred for 15 min, the solvents were removed on the rotovap, and MeOH (100 mL) was added again. The mixture was stirred for another 15 min and the MeOH removed on the rotovap again. SCX-silica (50 g) was added to the reaction mixture. The silica mixture was then loaded onto a filter funnel and flushed with methanol (400 mL), which was then subsequently flushed with 1 M ammonia solution in methanol (400 mL), which contained the desired product. The ammonia solution was collected and concentrated to give 2.24 g of the desired NH-pyrrolidne (50% yield). The crude NH-pyrrolidine was taken to the next step without further purification. A solution of 5-chloro-2,4-bis(methoxymethoxy)benzoic acid (12, 2.58 g, 9.34 mmol), HOBT (2.18 g, 10.3 mmol), crude NH-pyrrolidine (2.18 g, 9.34 mmol), EDCI (1.97 g, 10.3 mmol), and NMM (1.1 mL, 10.3 mmol) in anhydrous DMF (20 mL)

was heated at 50 °C for 3 h and then allowed to react for 16 h at room temperature. The reaction mixture was partitioned between EtOAc (50 mL) and aq. $NaHCO_3$ (50 mL). The organic phase was separated, washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated to dryness. The residue was dissolved in methanol (5 mL), and HCl was added (5 mL of 0.5 M in MeOH). The reaction was stirred at 50 °C for 4 h. The reaction mixture was then concentrated and purified by silica gel chromatography using a gradient of 30−50% EtOAc in hexanes. Collection and concentration of the pure fractions afforded 1.98 g (78%) of compound **14** as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.69−1.99 (m, 3 H), 2.30−2.48 (m, J = 7.54 Hz, 1 H), 3.48−3.91 (m, 2 H), 5.09−5.27 (m, 1 H), 6.51 (s, 1 H), 7.13 (s, 1 H), 7.47 (d, J = 7.72 Hz, 2 H), 7.82 (d, J = 8.10 Hz, 2 H), 9.91−10.12 (m, 2 H), 10.22 (s, 1 H). APCI-MS: m/z 346 (M^+ + H).

Synthesis of Library 5{13}{*1*−*89*}. Stock solutions of amines **5**{*1*−*89*} were prepared at a concentration of 0.4 M in anhydrous dichloromethane (DCM). A 0.4 M solution of **13** was prepared in DCM, as well as a 0.1 M solution of acetic acid in DCM. Finally, a 0.16 M suspension of $NaBH(OAc)_3$ in DCM was prepared. A set of 89 10 × 75 mm test tubes was arranged in an array format. Using an Eppendorf pipet, 210 μL (0.084 mmol, 1.05 equiv) of the amine solution, 200 μL (0.080 mmol, 1.0 equiv) of 13 and 80 μL (0.008 mmol, 0.1 equiv.) of the acetic acid solution were placed into the appropriate test tube. The test tubes were sealed with parafilm and placed on a shaker at room temperature for 1 h. Using an Eppendorf pipet, 750 μL (0.12 mmol, 1.5 equiv) of the $NaBH(OAc)_3$ solution was placed into each test tube, and the tubes were resealed with parafilm and placed on a shaker at room temperature for 2 h. The excess $NaBH(OAc)_3$ was quenched by the addition of 500 μL of methanol to each test tube and shaking further for 1 h. The volatile solvents were evaporated using the GeneVac apparatus. Heating was not required for removal of dichloromethane/methanol; 1340 μL of DMSO (containing 0.01% BHT) was added to each test tube, and the crude reaction mixtures were purified via reverse phase HPLC as described in ref 22.

Synthesis of Library 5{14}{*1*−*89*}. Stock solutions of amines **5**{*1*−*89*} were prepared at a concentration of 0.4 M in anhydrous DMSO. A 0.2 M solution of 14 in DMSO, as well as a 0.6 M suspension of $NaBH(OAc)_3$ in DMSO were prepared. A set of 89 10 × 75 mm test tubes was arranged in an array format. Using an Eppendorf pipet, 200 μL (0.08 mmol, 1.0 equiv) of the amine solution, 400 μL (0.080 mmol, 1.0 equiv) of **14**, and 333 μL (0.20 mmol, 2.5 equiv) of the suspension of $NaBH(OAc)_3$ were placed into the appropriate test tube. The test tubes were sealed with parafilm and placed on a shaker at room temperature for 1 h. The excess $NaBH(OAc)_3$ was quenched by the addition of 200 μL of methanol to each test tube and shaking further for 1 h; 267 μL of DMSO (containing 0.01% BHT) was added to each test tube and the crude reaction mixtures were purified via reverse phase HPLC and analyzed as described in ref 22.

***rac*-4-Chloro-6-[(2-{4-[(33-difluoropyrrolidin-1-yl)methyl]-phenyl}pyrrolidin-1-yl)carbonyl]benzene-1,3-diol (±)-15, (+)-15, (−)-15.** 3,3-Difluoropyrrolidine-HCl (137 mg, 0.95 mmol) was dissolved in DMSO (3 mL). Aldehyde **14** (300 mg, 0.86 mmol) was added, followed by $NaBH(OAc)_3$ (460 mg, 2.2 mmol), and the reaction was allowed to stir at room temperature for 16 h. Without removing the DMSO, purification was accomplished via silica gel chromatography eluting with a gradient of 1% to 5% MeOH in DCM to afford 390 mg (100%) as a white solid. ^{1}H NMR (400 MHz, chloroform-d): δ ppm 1.85−2.00 (m, 3 H), 2.00−2.13 (m, 1 H), 2.19−2.35 (m, 2 H), 2.34−2.49 (m, 1 H), 2.73 (dd, J = 6.80 Hz × 2, 2 H), 2.88 (t, J = 13.22 Hz, 2 H), 3.62 (s, 2 H), 3.87−3.97 (m, 1 H), 3.95−4.06 (m, 1 H), 5.24 (br. s., 1 H), 6.56 (s, 1 H), 7.22 (d, J = 7.30 Hz, 2 H), 7.30 (d, J = 7.05 Hz, 2 H), 7.52 (br. s., 1 H), 11.53 (br. s., 1 H). (±)-**15** was resolved using chiral SFC chromatography. (+)-**15** $[\alpha]_D$ = 134.9°, 100% ee; the ^{1}H NMR matched that of the racemic material. (−)-**15** $[\alpha]_D$ = −139.6°, 100% ee; ^{1}H NMR matched that of the racemic material.

***rac*-4-Chloro-6-[(2-{4-[(33-difluoroazetidin-1-yl)methyl]-phenyl}pyrrolidin-1-yl)carbonyl]benzene-13-diol (±)-16.** 3,3-Difluoroazetidine-HCl (123 mg, 0.95 mmol) was dissolved in DMSO (3 mL). Aldehyde **14** (295 mg, 0.85 mmol) was added, followed by $NaBH(OAc)_3$ (460 mg, 2.2 mmol), and the reaction mixture was allowed to stir at room temperature for 16 h. Purification was accomplished via silica gel chromatography, eluting with a gradient of 1−5% MeOH in DCM to afford 324 mg (90%) as a white solid. ^{1}H NMR (400 MHz, chloroform-d): δ ppm 1.85−2.14 (m, 4 H), 2.42 (br. s., 1 H), 3.59 (dd, J = 11.96 Hz, 4 H), 3.73 (s, 2 H), 3.86−3.99 (m, 1 H), 3.96−4.07 (m, 1 H), 5.24 (br. s., 1 H), 6.57 (br. s., 1 H), 7.17−7.25 (m, 2 H), 7.27−7.32 (m, 2 H), 7.34−7.66 (m, 1 H), 11.53 (br. s., 1 H). (±)-**16** was resolved using chiral SFC chromatography. (+)-**16** $[\alpha]_D$ = 136.1°, 100% ee; ^{1}H NMR matched that of the racemic material. (−)-**16** $[\alpha]_D$ = −136.3°, 100% ee; the ^{1}H NMR matched that of the racemic material.

***rac*-4-Chloro-6-({2-[4-(morpholin-4-ylmethyl)phenyl]pyrrolidin-1-yl}carbonyl)benzene-1,3-diol (±)-17.** Morpholine (123 mg, 1.42 mmol) was dissolved in DMSO (4 mL). Aldehyde **14** (445 mg, 1.29 mmol) was added, followed by $NaBH(OAc)_3$ (682 mg, 3.22 mmol), and the reaction was allowed to stir at room temperature for 16 h. Purification was accomplished via silica gel chromatography eluting with a gradient of 1% to 5% MeOH in DCM to afford 378 mg (100%) as a white solid. ^{1}H NMR (400 MHz, chloroform-d): δ ppm 1.88−1.99 (m, 2 H), 2.07 (d, J = 13.35 Hz, 2 H), 2.41−2.51 (m, 5 H), 3.51 (br. s., 2 H) 3.68−3.76 (m, 4 H), 3.86−3.97 (m, J = 7.05 Hz, 1 H), 3.97−4.06 (m, 1 H), 5.24 (s, 1 H), 6.55 (s, 1 H), 7.22 (d, J = 7.05 Hz, 2 H), 7.32 (d, J = 7.81 Hz, 3 H), 11.49 (br. s., 1 H). (±)-**17** was resolved using chiral SFC chromatography. (+)-**17** $[\alpha]_D$ = 145.2°, 100% ee; the ^{1}H NMR matched that of the racemic material. (−)-**17** $[\alpha]_D$ = −149.4°, 100% ee; the ^{1}H NMR matched that of the racemic material.

(*R*)-(5-Chloro-2,4-dihydroxyphenyl)(2-(6-(trifluoromethyl)pyridin-3-yl)pyrrolidin-1-yl)methanone (19). To a solution of previously de-Boc-protected **30** (50 mg, 0.23 mmol, de-

Boc-protected using 4 N HCl in dioxane) in DMF (5 mL) was added **12** (64 mg, 0.23 mmol), HOBt (63 mg, 0.46 mmol), NMM (0.51 mL, 0.46 mmol), and EDCI (89 mg, 0.46 mmol). The reaction mixture was allowed to stir at room temperature for 12 h. Water (5 mL) was added, and the product was extracted into EtOAc. After the organic layer was dried ($MgSO_4$) and the solution was concentrated to dryness, the MOM groups were removed as follows. HCl (0.91 mL of 4 N in 1,4-dioxane, 3.5 mmol) was added to a DCM solution (5 mL) of the residue from above After 5 h, the solvents were evaporated and the acid was neutralized with saturated aqueous $NaHCO_3$. Water was added, and the product was extracted using EtOAc (2 × 50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated to get an oil. Purification via silica gel chromatography provided the desired product 63 mg (70%) as a white foam. ^{1}H NMR (400 MHz, MeOD): δ ppm 1.l71−2.15 (m, 3H), 2.54 (d, J = 5.31 Hz, 1H), 3.49−3.75 (m, 1H), 3.83−4.04 (m, 1H), 5.15−5.47 (m, 1H), 6.50 (s, 1H), 7.30 (s, 1H), 7.76 (d, J = 5.05 Hz, 1H), 8.02 (s, 1H), 8.73 (s, 1H).

4-Chloro-6-({(2*R*)-2-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-1-yl}carbonyl)benzene-1,3-diol (20). To a solution of 1-Boc-pyrrolidine (976 mg, 5.70 mmol, 1.0 equiv) and (−)-sparteine (1.34 g, 5.70 mmol) in 12 mL anhydrous MTBE at −78 °C was added sec-butyl lithium (4.07 mL of 1.4 M in cyclohexane, 5.70 mmol) dropwise, keeping temperature below −68 °C. The resulting solution was stirred for 3 h at −78 °C. A solution of zinc chloride (3.42 mL of 1.0 M in ether, 3.42 mmol) was added with rapid stirring, keeping temperature below −68 °C. A light suspension formed and stirring was continued for 30 min at −78 °C. The reaction mixture was then warmed up to room temperature. After the mixture was stirred for additional 30 min at room temperature, 2-bromo-5-(trifluoromethyl)pyridine (1.09 g, 4.84 mmol,), palladium acetate (51 mg, 0.23 mmol), and tri-*tert*-butylphosphine tetrafluoroborate (83 mg, 0.28 mmol) were added. The resulting reaction mixture was stirred overnight at room temperature. During the course of the reaction, precipitates formed. To facilitate the filtration, concentrated NH_4OH (0.35 mL) was added, and the mixture was stirred for 1 h. The resulting slurry was filtered through Celite and washed with 60 mL of MTBE. The resulting organic layer was washed with water (1 × 50 mL), dried over sodium sulfate, and concentrated to dryness. The residue was purified using flash chromatography eluting with 20% ethyl acetate in hexanes to afford *tert*-butyl (2*R*)-2-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidine-1-carboxylate (0.88 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.90 (s, 1 H), 8.17 (t, J = 9.09 Hz, 1 H), 7.49 (d, J = 8.34 Hz, 0.62 H), 7.44 (d, J = 8.34 Hz, 0.40 H), 4.90 (d, J = 7.33 Hz, 0.40 H), 4.80−4.88 (m, 0.63 H), 3.41−3.60 (m, 2 H), 2.24−2.42 (m, 1 H), 1.77−1.94 (m, 3 H), 1.38 (s, 3.59 H), 1.07 (s, 5.45 H). LCMS: $(M + H)^+$ = 317.20. *tert*-Butyl (2*R*)-2-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidine-1-carboxylate (200 mg, 0.632 mmol) was dissolved in TFA (4 mL) and stirred for 16 h. The excess TFA was removed in vacuo, and the resulting residue was neutralized with Et_3N. The resulting 2-arylpyrrolidine was dissolved in DMF (2 mL). **12** (175 mg, 0.632 mmol, 1.0 equiv), HATU (264 mg, 0.695 mmol), and Et_3N (353 uL, 2.53 mmol) were added as a solution in DMF (2 mL). The resulting reaction mixture was heated at 60 °C for 5 h. The reaction mixture was then diluted with water (10 mL) and extracted with isopropyl acetate (20 mL). The organic phase was then separated, washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated to dryness. The resulting residue was treated with HCl (4 mL of 4.0 M in dioxane) for 3 h to complete the deprotection of the MOM groups. After removal of the solvents in vacuo, the resulting residue was purified via flash chromatography, eluting with 50% ethyl acetate in hexanes to afford **20** as a powder (197 mg, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.49 (s, 0.79 H), 10.43 (s, 0.79 H), 10.16 (s, 0.24 H), 9.99 (s, 0.22 H), 8.90 (s, 0.78 H), 8.77 (s, 0.22 H), 8.16 (d, J = 7.58 Hz, 0.79 H), 7.99 (s, 0.22 H), 7.63 (d, J = 8.08 Hz, 0.78 H), 7.22 (s, 1 H), 6.57 (s, 0.81 H), 6.39 (s, 0.46 H), 5.15−5.25 (m, 0.78 H), 4.99 (s, 0.23 H), 3.66−3.77 (m, 1 H), 3.48−3.59 (m, 1 H), 2.31−2.46 (m, 1 H), 1.79−1.94 (m, 3 H). CHN Calcd for $C_{17}H_{14}ClF_3N_2O_3$ + 0.11 hexanes: C, 53.53; H, 3.95; N, 7.07. Found: C, 53.62; H, 3.98; N, 6.87. LCMS: $(M + H)^+$ = 387.00.

4-Chloro-6-{[(2*R*)-2-(2,6-dimethylpyridin-3-yl)pyrrolidin-1-yl]carbonyl}benzene-1,3-diol (21). To a solution of 1-Boc-pyrrolidine (976 mg, 5.70 mmol) and (−)-sparteine (1.34 g, 5.70 mmol) in anhydrous MTBE (12 mL) at −78 °C was added sec-butyl lithium (4.07 mL of 1.4 M in cyclohexane, 5.70 mmol) dropwise, keeping temperature below −68 °C. The resulting reaction was stirred for 3 h at −78 °C. A solution of zinc chloride (3.42 mL of 1.0 M in ether, 3.42 mmol) was added dropwise with rapid stirring, keeping temperature below −68 °C. A light suspension formed, and stirring was continued for 30 min at −78 °C, and then 30 min at room temperature. 3-Bromo-2,6-dimethylpyridine (0.90 g, 4.84 mmol), palladium acetate (51 mg, 0.23 mmol), and tri-*tert*-butylphosphine tetrafluoroborate (83 mg, 0.28 mmol). The resulting reaction mixture was stirred for 16 h at room temperature. During the course of the reaction, precipitate formed. To facilitate filtration, concentrated NH_4OH (0.35 mL) was added, and the mixture stirred for 1 h. The resulting slurry was filtered through Celite and washed with MTBE (60 mL). The organic phase was washed with water (50 mL), dried over sodium sulfate, and concentrated to dryness. The resulting residue was purified via flash chromatography eluting with 20% ethyl acetate in hexanes to afford *tert*-butyl (2*R*)-2-(2,6-dimethylpyridin-3-yl)pyrrolidine-1-carboxylate (0.65 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.28 (d, J = 7.83 Hz, 0.57 H), 7.20 (d, J = 7.58 Hz, 0.41 H), 6.97−7.07 (m, 1 H), 4.90 (d, J = 6.32 Hz, 0.40 H), 4.81−4.88 (m, 0.57 H), 3.50−3.61 (m, 1 H), 3.39−3.50 (m, 1 H), 2.42 (s, 3 H), 2.38 (s, 3 H), 2.19−2.35 (m, 1 H), 1.67−1.89 (m, 2 H), 1.50−1.66 (m, 1 H), 1.37 (s, 4 H), 1.08 (s, 5 H). LCMS: $(M + H)^+$ = 277.20. *tert*-Butyl (2*R*)-2-(2,6-dimethylpyridin-3-yl)pyrrolidine-1-carboxylate (200 mg, 0.632 mmol) was dissolved in TFA (4 mL) and stirred for 16 h. After removal of the excess TFA in vacuo, the resulting residue was neutralized with Et_3N. The 2-arylpyrrolidine was dissolved in DMF (2 mL).

5-Chloro-2,4-bis(methoxymethoxy)benzoic acid (175 mg, 0.632 mmol), HATU (264 mg, 0.695 mmol), and Et_3N (353 uL, 2.53 mmol) were added as a solution in DMF (2 mL). The resulting reaction mixture was heated at 60 °C for 5 h. The reaction mixture was then diluted with water (10 mL), and the product was extracted with isopropyl acetate (20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over sodium sulfate. After it was concentrated to dryness, the residue was treated with HCl (4 mL of 4.0 M in dioxane), and the reaction mixture was stirred for 3 h. After removal of the solvents in vacuo, the resulting residue was purified by preparative HPLC to afford **21** as a white solid (8.5 mg, 3.9%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.55 (br. s., 2 H), 7.52 (d, J = 7.33 Hz, 1 H), 7.21 (s, 1 H), 7.00 (d, J = 8.08 Hz, 1 H), 6.54 (s, 1 H), 5.08−5.24 (m, 1 H), 3.69−3.82 (m, 1 H), 3.43−3.55 (m, 1 H), 2.48 (s, 3 H), 2.37 (s, 4 H), 1.75−1.87 (m, 2 H), 1.52−1.69 (m, 1 H). LCMS: $(M + H)^+ = 347.00$.

4-Chloro-6-({(2*R*)-2-[4-(methylsulfonyl)phenyl]pyrrolidin-1-yl}carbonyl)benzene-13-diol (22). To a solution of 1-Boc-pyrrolidine (325 mg, 1.9 mmol) and (−)-sparteine (0.44 g, 1.9 mmol) in 12 mL anhydrous MTBE at −78 °C was added sec-butyl lithium (1.35 mL of 1.4 M cyclohexane, 1.9 mmol) dropwise, keeping the temperature below −68 °C. The resulting reaction solution was stirred for 3 h at −78 °C. A solution of zinc chloride (3.4 mL of 0.5 M in THF, 0.30 mmol) was added dropwise to the above reaction mixture with rapid stirring, keeping the temperature below −68 °C. A light suspension was formed. Stirring was continued for 30 min at −78 °C, and the reaction mixture was warmed to room temperature. After it was stirred for an additional 30 min at room temperature, the reaction solution was transferred via a syringe to a flask containing a mixture of 1-bromo-4-(methylsulfonyl)benzene (353 mg, 1.5 mmol), palladium acetate (51 mg, 0.23 mmol), and tri-tert-butylphosphine tetrafluoroborate (83 mg, 0.28 mmol). The resulting reaction mixture was stirred overnight at room temperature. During the course of the reaction, the color of the reaction mixture became dark, and precipitates formed. To facilitate the filtration, concentrated NH_4OH (0.35 mL) was added, and the mixture was stirred for 1 h. The resulting slurry was filtered through Celite and washed with 60 mL MTBE. The resulting organic layer was washed with 1 M HCl (50 mL) and water (2 × 50 mL), dried over sodium sulfate, and concentrated to dryness. The residue was purified via silica gel chromatography eluting with hexanes:EtOAc (80:20) to afford the desired Boc-protected pyrrolidine adduct as an oil (0.385 g, 26%). ^{1}H NMR (400 MHz, DMSO-d_6; compound exists as a 1.25:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §) 1.13 (br. s., 9 H*§) 1.36 (br. s.,9 H§) 1.75 (br. s., 3 H*, 3 H§) 2.34 (br. s., 1 H*, 1 H§) 3.19 (br. s., 3 H*, 3 H§) 3.51 (br. s., 2 H*, 2 H§) 4.81 (br. m., 1 H*) 4.91 (br.m., 1 H§) 7.44 (br. s., 2 H*, 2 H§) 7.87 (br. s., 2 H*, 2 H§); APCI-MS: m/z 226 (M^+ + H). The resulting oil was dissolved in dichloromethane (5 mL) and TFA (2 mL) was added. The reaction was stirred overnight at room temperature then concentrated and used in the next step without any further purification. A solution of 5-chloro-2,4-bis(methoxymethoxy)-benzoic acid (**12**, 107 mg, 0.38 mmol), HOBT (57 mg, 0.38 mmol), (*R*)-2-(4-(methylsulfonyl)phenyl)pyrrolidine (87 mg, 0.38 mmol), EDCI (81 mg, 0.42 mmol), and NMM (0.047 mL, 0.42 mmol) in 6 mL anhydrous DMF was heated at 50 °C for 3 h then at room temperature for 16 h. The reaction mixture was partitioned between EtOAc (50 mL) and aq $NaHCO_3$ (50 mL). The organic phase was separated, washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated to dryness. To the residue dissolved in methanol (5 mL) was added HCl in methanol (5 mL of 0.5 M), and the mixture was stirred at 50 °C for 4 h. The reaction mixture was concentrated and purified by silica gel chromatography (gradient elution 30−50% EtOAc in hexanes) to give the desired final product as a white solid (68 mg, 45%). ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 0.71−1.31 (br m), 1.34−1.66 (br m), 1.77−2.22 (br m), 2.37−2.64 (br m), 2.89−3.09 (br m), 3.56−3.83 (br m), 3.86−4.21 (br m), 5.20−5.40 (br m), 5.55−6.07 (br m), 6.43−6.74 (br m), 7.36−7.61 (br m), 7.80−8.05 (br m), 11.16−11.45 (br m). APCI-MS: m/z 396 (M^+ + H).

4-[(2*R*)-1-(5-chloro-24-dihydroxybenzoyl)pyrrolidin-2-yl]-3-methylbenzonitrile (23). To a solution of 1-Boc-pyrrolidine (325 mg, 1.9 mmol) and (−)-sparteine (0.445 g, 1.9 mmol) in 12 mL anhydrous MTBE at −78 °C was added sec-butyl lithium (1.35 mL of 1.4 M in cyclohexane, 1.9 mmol) dropwise, keeping the temperature below −68 °C. The resulting reaction solution was stirred for 3 h at −78 °C. A solution of zinc chloride (3.4 mL of 0.5 M in THF, 0.298 mmol) was added dropwise with rapid stirring, keeping the temperature below −68 °C. A light suspension formed, and the reaction mixture was held at −78 °C for 30 min and then warmed to room temperature. After it was stirred for an additional 30 min at room temperature, the reaction solution was transferred via syringe to a flaskcontaining a mixture of 4-bromo-3-methylbenzonitrile (350 mg, 1.5 mmol), palladium acetate (51 mg, 0.23 mmol), and tri-*tert*-butylphosphine tetrafluoroborate (83 mg, 0.28 mmol). The resulting reaction mixture was stirred overnight at room temperature. During the course of the reaction, the color of the reaction mixture became dark and precipitates formed. To facilitate the filtration, concentrated NH_4OH (0.35 mL) was added, and the mixture was stirred for 1 h. The resulting slurry was filtered through Celite and washed with 60 mL MTBE. The resulting organic layer was washed with 1 M HCl (50 mL) and water (2 × 50 mL), dried over sodium sulfate, and concentrated to dryness. The resulting residue was purified by silica gel chromatography eluting with hexanes:EtOAc (80:20) to afford the Boc-protected pyrrolidine adduct as an oil (0.385 g, 26%). The resulting oil was dissolved in dichloromethane (5 mL), and TFA (2 mL) was added; the mixture was stirred overnight at room temperature. The reaction was concentrated down to afford (*R*)-3-methyl-4-(pyrrolidin-2-yl)benzonitrile, which was used in the next step without further purification. A solution of 5-chloro-2,4-bis(methoxymethoxy)benzoic acid (**12**, 210 mg, 0.760 mmol), HOBT (103 mg, 0.760 mmol), (*R*)-3-methyl-4-(pyrrolidin-2-yl)benzonitrile (118 mg, 0.634 mmol), EDCI (146 mg, 0.760 mmol), and NMM (0.084 mL, 0.760 mmol, 1.1 equiv) in 6 mL anhydrous DMF was heated at 50 °C for 3 h then

16 h at room temperature. The reaction mixture was partitioned between ethyl acetate (50 mL) and aq. $NaHCO_3$ (50 mL). The organic phase was separated, washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated to dryness. The residue was dissolved in methanol (5 mL), and HCl in methanol (5 mL of 0.5M) was added. The reaction was stirred at 50 °C for 4 h. The reaction mixture was concentrated and purified by silica gel chromatography (gradient elution 30−50% EtOAc in hexanes) to give the desired final product as a white solid (41 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.47−1.69 (bm, 1 H), 1.76−1.92 (bm, 2 H), 1.99−2.07 (bm, 0.8 H), 2.33−2.43 (bm, 3 H), 3.43−3.59 (bm, 1.2 H), 3.69−3.89 (bm, 1.2 H), 5.10−5.18 (bm, 0.2 H), 5.24 (t, J = 7.18 Hz, 0.8 H), 6.35 (s, 0.2 H), 6.48 (s, 0.2 H), 6.56 (s, 0.8 H), 7.22 (s, 1 H), 7.40−7.54 (m, 1 H), 7.55−7.74 (m, 1 H), 10.02−10.23 (m, 0.4 H), 10.38−10.55 (m, 1.6 H). APCI-MS: m/z 357 (M^+ + H).

4-Chloro-6-[(2-{4-[(4,4-difluoropiperidin-1-yl)carbonyl]-2-methylphenyl}pyrrolidin-1-yl)carbonyl]-benzene-1,3-diol (25). Boc-ester **27** was hydrolyzed to the acid by dissolving LiOH (354 mg, 15 mmol) in water (7.6 mL) and then adding a solution of **27** (1.3 g, 4.1 mmol) in MeOH (15 mL) dropwise to the LiOH and allowing the reaction to stir overnight. The solvents were removed, and the residue was dissolved in water (30 mL) and neutralized with 1 N HCl to pH = 4. A white precipitate formed, which was filtered, washed with water several times, and dried to afford the acid (1.2 g, 95%). The acid (296 mg, 0.969 mmol) and 4,4-difluoropiperidine (197 mg, 1.25 mmol) were mixed in DMF (9 mL). Et_3N (0.41 mL, 2.9 mmol) was added, followed by HATU (412 mg, 1.08 mmol). The reaction was stirred at 60 °C, for 24 h. Ice water (10 mL) was added, and a solid precipitated from solution. The solid was filtered and washed with water. The crude yield of the Boc-amide intermediate (MW = 408) was 346 mg (88%), and this material was taken on to the next step. The crude Boc-amide intermediate (346 mg, 0.85 mmol) was dissolved in DCM (5 mL), and TFA (5 mL) was added. After the mixture was stirred at room temperature for 18 h, the solvents were removed to afford (*R*)-4,4-difluoro-1-(4-(pyrrolidin-2-yl)benzyl)piperidine (162 mg, 54%), which was taken further without purification. (*R*)-4,4-difluoro-1-(4-(pyrrolidin-2-yl)-benzyl)piperidine (162 mg, 0.46 mmol) was dissolved in DMF (5 mL). MOM protected acid **12** (130 mg, 0.46 mmol), Et_3N (353 uL, 2.53 mmol), and HATU (170 mg, 0.46 mmol) were added, and the resulting reaction mixture was heated at 60 °C for 5 h. The reaction mixture was then diluted with water (10 mL), and extracted with ethyl acetate (20 mL). The organic phase was separated, washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated to dryness. The resulting residue was treated with HCl (4 mL of 4.0 M in dioxane, 16 mmol) for 3 h to complete the deprotection of the MOM groups. After removal of the solvents in vacuo, the resulting residue was purified via flash chromatography eluting with 50% ethyl acetate in hexanes to afford **25** as a powder (271 mg, 81% for the last 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.48 (d, J = 6.57 Hz, 2 H), 10.25 (s, 0.40 H), 10.19 (s, 0.38 H), 7.37 (d, J = 7.83 Hz, 1 H), 7.13−7.28 (m, 4 H), 7.01−7.10 (m, 1 H), 6.50−6.59 (m, 1.73 H), 6.35 (s, 0.44 H), 5.25 (t, J = 6.69 Hz, 1 H), 5.18 (br. s., 0.47 H), 3.74−3.86 (m, 2 H), 3.64−3.74 (m, 2 H), 3.43−3.55 (m, 4 H), 2.30−2.47 (m, 5 H), 1.94−2.11 (m, 4 H), 1.77−1.94 (m, 2 H), 1.54−1.73 (m, 2 H).

4-[(2-{4-[(4,4-Difluoropiperidin-1-yl)carbonyl]-2-methylphenyl}pyrrolidin-1-yl)carbonyl]-6-methylbenzene-13-diol (26). To a 40 mL scintillation vial was added (*R*)-4,4-difluoro-1-(4-(pyrrolidin-2-yl)benzyl)piperidine (synthesized as described above) (162 mg, 0.525 mmol) and 2,4-dihydroxy-5-methyl benzoic acid (80 mg, 0.48 mmol), followed by DMF (2.4 mL). Et_3N (0.2 mL, 1.4 mmol) was added, followed by HATU (190 mg, 0.49 mmol). After 3 h, Et_2O (30 mL) and saturated sodium bicarbonate (20 mL) were added. The product was extracted into Et_2O (3 × 10 mL), and the combined organic extracts were washed with sodium bicarbonate (3 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). After the organic extract was dried ($MgSO_4$) and concentrated to an oil, the product was purified via silica gel chromatography to afford 46 mg (19%) as a white solid. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 1.49−2.55 (m, 14 H), 3.45−4.02 (m, 6 H), 3.99−4.11 (m, 1 H), 5.42 (br. s., 1 H), 6.32 (s, 1 H), 7.14−7.29 (m, 3 H), 7.29−7.43 (m, 1 H), 11.34 (br. s., 1 H).

***tert*-Butyl (2*R*)-2-[4-(Methoxycarbonyl)-2-methylphenyl]pyrrolidine-1-carboxylate (27).** To a solution of 1-Boc-pyrrolidine (1.0 g, 5.8 mmol) and (−)-sparteine (1.4 g, 5.8 mmol) in 12 mL anhydrous MTBE at −78 °C was added sec-butyl lithium (4.2 mL in 1.4 M in cyclohexane, 5.8 mmol) dropwise keeping the temperature below −68 °C. The resulting solution was stirred for 3 h at −78 °C. A solution of zinc chloride (7.0 mL of 0.5 M in THF, 3.50 mmol) was added dropwise with rapid stirring, keeping the temperature below −68 °C. A light suspension formed, and stirring was continued for 30 min at −78 °C and then at room temperature for 30 min longer. Solid 4-bromo-3-methyl benzoic acid methyl ester (1.14 g, 4.96 mmol), $Pd(OAc)_2$ (53 mg, 0.23 mmol), and tritertbutylphosphine tetrafluoroborate (85 mg, 0.29 mmol) were added sequentially. The resulting reaction mixture was stirred at rt for 16 h. To facilitate the filtration, NH_4OH (1.0 mL) was added, and the mixture was stirred for 1 h. The resulting slurry was filtered through Celite and washed with 20 mL MTBE. The resulting filtrate was washed with 1 M HCl (20 mL) and water (20 mL), and the organic layer was dried over sodium sulfate and concentrated to dryness. After silica gel purification using 20% ethyl acetate in hexanes, the desired product (1.07 g, 67.5% yield) was obtained as an oil. Analysis by chiral SFC indicated a 96:4 er. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.70−7.79 (m, 2 H), 7.19 (d, J = 7.83 Hz, 0.68 H), 7.12 (d, J = 7.83 Hz, 0.38 H), 4.98 (d, J = 6.06 Hz, 0.38 H), 4.92 (dd, J = 7.45, 5.43 Hz, 0.65 H), 3.83 (s, 3 H), 3.42−3.63 (m, 2 H), 2.24−2.42 (m, 4 H), 1.68−1.90 (m, 2 H), 1.49−1.65 (m, 1 H), 1.38 (s, 3.65 H), 1.04 (s, 5.30 H).

Large Scale Parallel Synthesis Procedure for the Preparation of Boc-Pyrrolidines 28−34. A 1 L three-neck flask was equipped with a large stir bar, an internal thermometer, and an addition funnel. The flask was charged

with *N*-Boc pyrrolidine (11 mL, 64 mmol). MTBE (130 mL) was added, followed by (−)-sparteine (15 mL, 64 mmol). The reaction was cooled to −78 °C, and s-BuLi (58 mL of 1.1 M in cyclohexane, 64 mmol) was added via the addition funnel keeping internal temperature below −68 °C. The reaction was allowed to stir at −78 °C for 5 h. A solution of $ZnCl_2$ (128 mL of 0.5 M in THF) was added keeping the temperature below −68 °C. The suspension was aged at −78 °C for 30 min and then allowed to warm up to 20 °C and allowed to stir at room temperature overnight (16 h). The total volume of the reaction mixture was 342 mL for a final theoretical concentration of the Zn-Boc-pyrrolidine reagent equal to 0.187 M. In the mean time, to prepare for the coupling reaction, nine labeled 40 mL scinitiallation vials were marked at the 28 mL mark and equipped with a stir bar. In separate labeled 10 mL scinitiallation vials, the aryl bromides (4.42 mmol) were weighed out and dissolved in THF (5 mL). The Negishi reagent (28 mL, 5.3 mmol) from the 1 L three neck flask was cannulated into the labeled scintillation vials under N_2. The THF solution of the aryl bromide was added to the Zn-Boc-pyrrolidine reagent, followed by the addition of $Pd(OAc)_2$ (50 mg, 0.22 mmol) and tri-*t*butyl phosphine-BF_4 (80 mg, 0.28 mmol) in one portion. The vials were capped and allowed to stir vigorously for 24 h at room temperature. Each reaction was diluted with MTBE (50 mL) and filtered through Celite washing with MTBE (2 × 25 mL). The organic layer was washed water saturated aq. NH_4Cl (2 × 25 mL), then washed with water (2 × 25 mL), and dried over sodium sulfate. After filtration, the products were purified either by flash chromatography or by reverse phase HPLC. The products were obtained with yields and analytical data as described below. The enantiomeric ratio was measured using chiral SFC (area %).

***tert*-Butyl (2*R*)-2-(4-Cyanomethyl-3-fluorophenyl)pyrrolidine-1-carboxylate (28). 28** was obtained in 44% yield as a white solid; er = 96:4. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1.4:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.22 (br. s., 9 H*), 1.46 (br. s., 9 H§), 1.79 (d, J = 5.56 Hz, 1 H*, 1H§), 1.84−1.93 (m, 2 H*, 2H§), 2.32 (m, 1H*, 1H§), 3.61 (d, J = 6.06 Hz, 2 H*, 2H§), 3.69−3.78 (m, 2 H*, 2H§), 4.73−4.81 (m, 1 H*), 4.87−4.95 (m, 1 H§), 6.93 (d, J = 10.61 Hz, 1H*, 1H§), 7.01 (d, J = 7.83 Hz, 1H*, 1H§), 7.36 (t, J = 7.83 Hz, 1H*, 1H§). LCMS: $(M + H)^+ = 305$.

***tert*-Butyl (2*R*)-2-(4-Cyano-dimethyl-methylphenyl)pyrrolidine-1-carboxylate (29). 29** was obtained in 44% yield as a white solid; er = 99:1. ^{1}H NMR (400 MHz, $CDCl_3$; ^{1}H NMR; compound exists as a 1.4:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.18 (br. s., 9 H*), 1.38−1.52 (m, 9 H§), 1.72 (s, 6 H*, 6 H§), 1.77−1.94 (m, 3 H*, 3 H§), 2.31 (br. s., 1 H*, 1 H§), 3.49−3.68 (m, 2 H*, 2 H§), 4.77 (br. s., 1 H*), 4.95 (br. s., 1 H§), 7.19 (d, J = 8.31 Hz, 2 H*, 2 H§), 7.36−7.46 (m, 2 H*, 2 H§). LCMS: $(M + H)^+ = 315$.

***tert*-Butyl (2*R*)-2-(6-Trifluoromethyl-pyridin-3-yl)pyrrolidine-1-carboxylate (30). 30** was obtained in 54% yield as a white solid; er = 96:4. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1.3:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.11−1.29 (m, 9 H*), 1.46 (d, J = 7.33 Hz, 9 H§), 1.79−1.87 (m, 1 H*, 1 H§), 1.87−1.99 (m, J = 6.28, 6.28, 6.13, 5.81 Hz, 2 H*, 2 H§), 2.40 (br. s., 1 H*, 1H§), 3.50−3.74 (m, 2 H*, 2 H§), 4.86 (br. s., 1 H*), 5.00 (br. s., 1 H§), 7.57−7.73 (m, 2 H*, 2 H§), 8.57 (s, 1 H*, 1 H§). LCMS $(M + H)^+ = 317$.

***tert*-Butyl (2*R*)-2-[4-(5-Methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]pyrrolidine-1-carboxylate (31). 31** was obtained in 62% yield as a white solid; er = 96:4. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.20 (br. s., 9 H*), 1.46 (br. s., 9 H§), 1.78−1.99 (m, 3 H*, 3 H§), 2.25−2.46 (m, 1 H*, 1 H§), 2.63 (s, 3 H*, 3 H§), 3.54−3.71 (m, 2 H*, 2 H§), 4.81 (br. s., 1 H*), 4.98 (br. s., 1 H§), 7.28 (d, J = 9.09 Hz, 2 H*, 2 H§), 8.00 (d, J = 8.34 Hz, 2 H*, 2 H§). LCMS $(M + H)^+ = 330$.

***tert*-Butyl (2*R*)-2-(4-Cyano-dimethyl-methyl-3-fluorophenyl)pyrrolidine-1-carboxylate (32). 32** was obtained in 44% yield as a white solid; er = 99:1. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.14−1.30 (br. s., 9 H*), 1.47 (br. s., 9 H§), 1.79 (br. s., 6 H*, 6 H§), 1.83−1.94 (m, 2 H*, 2 H§), 2.22−2.40 (m, 1 H*, 1 H§), 3.49−3.68 (m, 2 H*, 2 H§), 4.76 (br. s., 1 H*), 4.92 (br. s., 1 H§), 6.92 (d, J = 12.88 Hz, 1 H*, 1 H§), 6.97 (dd, J = 8.08, 1.52 Hz, 1 H*, 1H§), 7.41 (t, J = 8.08 Hz, 1 H*, 1 H§). LCMS $(M + H)^+ = 333$.

***tert*-Butyl (2*R*)-2-(4-Methanesulfonylmethyl-phenyl)pyrrolidine-1-carboxylate (33). 33** was obtained in 48% yield as a white solid; er = 96:4. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.18 (br. s., 9 H*), 1.46 (br. s., 9 H§), 1.76−1.99 (m, 3 H*, 3 H§), 2.33 (br. s., 1 H*, 1 H§), 2.76 (s, 3 H*, 3 H§), 3.64 (br. s., 2 H*, 2 H§), 4.24 (br. s., 2 H*, 2 H§), 4.78 (br. s., 1 H*), 4.96 (br. s., 1 H§), 7.23 (d, J = 8.08 Hz, 2 H*, 2 H§), 7.35 (d, J = 8.08 Hz, 2 H*, 2 H§). LCMS $(M + H)^+ = 340$.

***tert*-Butyl (2*R*)-2-(4-Dimethylamino-3-fluorophenyl)pyrrolidine-1-carboxylate (34). 34** was obtained in 42% yield as a white solid; er = 96:4. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is designated as *, the minor rotamer is designated as §): δ ppm 1.11−1.30 (br. s., 9 H*), 1.45 (br. s., 9 H§), 1.73−1.98 (m, 3 H*, 3 H§), 2.27 (br. s., 6 H*, 6 H§), 2.31−2.41 (m, 1 H*, 1 H§), 3.48 (br. s., 4 H*), 3.60 (br. s., 4 H§), 4.73 (br. s., 1 H*), 4.92 (br. s., 1 H§), 6.85 (d, J = 10.86 Hz, 1 H*, 1 H§), 6.92 (d, J = 7.58 Hz, 1 H*, 1 H§), 7.21−7.31 (m, 1 H*, 1 H§). LCMS $(M + H)^+ = 323$.

Synthesis of Library 6{*1*−*14*}{27−34}. Stock solutions of Boc-pyrrolidines **27**−**34** were prepared at a concentration of 0.4 M in DCM. Four molar HCl in 1,4-dioxane (10 equiv) was added, and the reaction mixtures were stirred for 3 h at room temperature. MeOH was added if there were problems with solubility. After 3 h, the solutions were concentrated to dryness and then dissolved in the appropriate amount of DMF to form 0.4 M solutions

of the amine component; 0.2 M solutions of acids **6**{*1*−*14*} in DMF were prepared. A set of 10 × 75 mm test tubes were arranged in an array format. Using an Eppendorf pipet, 200 μL (0.08 mmol, 1.0 equiv) of the amine solution, 400 μL (0.080 mmol, 1.0 equiv) of the acid solution, and 333 μL (0.20 mmol, 2.5 equiv) of a 0.6 M Et_3N solution in DMF were placed into the appropriate test tube. The test tubes were sealed with parafilm and placed on a shaker at room temperature for 30 min. To each tube was added 200 μL (0.08 mmol, 1.0 equiv.) of a 0.4 M DMF solution of HATU (O-(7-azobenztriazol-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate), and the reaction mixtures were sealed with parafilm and placed on a shaker at room temperature for 16 h. The DMF was removed in vacuo using a GeneVac HT-12 on medium heat. To the residue was added 267 μL of DMSO (containing 0.01% BHT) and the crude reaction mixtures were purified via reverse phase HPLC and analyzed as described in ref 22.

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Supporting Information Available. Structural biology information and the structures of the amine building blocks used for library **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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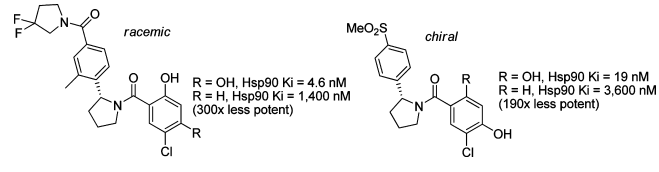

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